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54 Galenic formulations for oral use of rhelⁿ derivatives with delayed release for therapeutical use.

57 Several methods are disclosed for the preparation of oral pharmaceutical forms with delayed release of rh in and its derivatives.

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"Galenic formulations for oral use of rhein derivatives with delayed release for therapeutical use"

The derivatives of rhein of particularly of diacetylrhein are drugs endowed with a relevant antiarthrosic, analgesic and anti-inflammatory activity (Italian Patent No. 1098332).

The present invention relates to a number of formulations for oral use with slow release of dyacetylrhein and other derivatives of rhein for therapeutical purposes.

5 It is known that the more widespread solid pharmaceutical forms for oral use with delayed release of active ingredients may be reconducted to the following schemes:

a) comminution of the drug in particles of very small size by supporting them onto nuclei of inert substances. The microgranules thus obtained are thereafter coated with particular excipients (fatty substances and natural or synthetic waxes, plastic substances, etc.) so as to afford to the microgranules
10 different rates of drug release.

b) Absorption of the drug into suitable supports, (polymers, synthetic resins, etc.) so as to obtain insoluble complexes from which the active principle is gradually and slowly eluted under the action of the several biological factors of the gastro-enteric tract, such as pH, enzymatic activities, electrolytic concentration, etc.

15 c) Supporting onto an inert matrix capable of slowly swelling within the gastro-enteric duct (chemically modified celluloses, polysaccharides, etc.) thus permitting the release of the drug in gradual manner by diffusion.

d) Mixed technologies among those listed above which permit as well the delayed release of the drug.

20 The present invention relate to the preparation of rhein derivatives and particularly of dyacetylrhein derivatives in pharmaceutical formulations which permit a gradual and programmed release of the drug and such as to ensure a pharmacologically active hematic level throughout the period of 24 hours from the administration of the therapeutical dose of the drug. Some examples of formulation of rhein derivatives with slow release of the drug are hereinafter described, which have been controlled by the in vitro release test
25 as well as by determining the hematic levels of the drug after experimental administration to animals.

The examples hereinafter reported are not limiting and are described for the only purpose of better illustrate the content of the present invention.

30 **EXAMPLE 1**

500 g of dyacetylrhein with granule size of between 50 and 100 μ m are carefully admixed with 150 g of finely powdered saccharose and 150 g of mais starch; the mixture is finely ground and then supported onto 1000 g of micronuclei having about 0.4 mm of diameter by wetting with a solution containing 37.5 of
35 polyvinylpyrrolidone. The granulate is dried in an hot air oven, the dried granulate is sieved to prepare end granules of uniform size which are, in portions, coated in a basin with a 20% polyvinil pyrrolidone and 30% shellac solution isopropanol.

The number of applications of the coating solution onto the several portion of the granules is adjusted as a function of the release times as experimentally measured by means of the in vitro test.

40 The granules with different coating degrees are admixed as a function of the related release times measured so as to obtain in the same posologic unit (for example a capsule of hard gelatin) the desired amount of drug (for example 100 mg) and the release of the active principle within the programmed times (for instance 24 hours).

45 **EXAMPLE 2**

150g of dipropionylrhein are uniformly admixed with 300 g of lactose, 5 g of dispersed silicon dioxide, 15 g of magnesium stearate, 20 g of talc. Separately 350 g of dipropionylrhein are carefully admixed with
50 350 g of titanium dioxide, 115 g of polyvinylpyrrolidone and 25 g of triacetin. This mixture is wetted until a granulate is obtained which is dried in an hot air oven. The granules are coated in portions into a basin with an acetone solution of cellulose acetophtalate by adjusting the number of applications as a function of the release time to be obtained.

The mixture of the powders and the granulates with different coating degree are in turn admixed as a function of the related release times as determined in the in vitro test so as to obtain in the same posologic unit (for instance gelatin capsules, tablets, granulates, etc.) the desired amount of drug and the release of the active principle within the programmed time.

EXAMPLE 3

500 g of diacetylrhein are carefully admixed with 10 g of polyvinylpyrrolidone, 50 g of microcrystalline cellulose, 100 g of sodium citrate; the mixture is wet granulated with water and the granulate is dried in a hot air oven.

Separately 125 g of soya polisaccharides, 10 g of talc and 150 g of magnesium stearate are admixed and the mixture is wet granulated and dried. The two combined granulates are converted into tablets by means of a pressing machine and resulting tablets are coated by subsequent application of ethanol solution containing 40g of hydroxypropyl-methylcellulose, phthalate, 10 g of acetylated monoglyceride and 10 g of titanium dioxide.

"In vitro" release

The capsules obtained according to examples 1 and 3 are tested by means of an in vitro release test according to the method reported in U.S.P. XXI.

Active principle/ /capsules mg 100	Percent of released active principle				
	1 h	4 h	8 h	18	24 h
example No. 1	46.4	63.1	72.7	79.3	88.7
example No. 3	40.7	46.7	54.7	68.5	80.3

In "vivo" release

As an example the comparison between slow release diacetylrhein prepared according to example No. 1 and diacetylrhein in a formulation with immediate release, administered to 4-Beagle male sex dog having an average weight of 10 kg, fasted since about 16 hours before the test, is reported.

The diacetylrhein has been administered in the two pharmaceutical forms according to a "cross-over" experimental scheme at the dose of 20 ml/kg and with a washout time of a week.

The blood sampling has been carried out at the time 0 (basal) and after 1, 2, 4, 8, 12, 16, 20 and 20 hours after the treatment.

In the serum samples the rhein has been dosed by means of H.P.L.C..

The data reported in the figure 1 demonstrate that the slow release formulation, whilst does not essentially modify the bioavailability (AUC_{0-24h}) of diacetylrhein with respect to that of normal formulation, causes on the contrary a favourable change of the profile of the serum levels by extending the time of drug permanence in the hematic flow at therapeutical levels up to 24 hours.

Claims

1. Pharmaceutical composition containing rhein or a derivative thereof, particularly diacetylrhein or dipropionylrhein, as the active ingredient, characterized by being in a slow release pharmaceutical form.

5 2. Pharmaceutical composition according to claim 1, characterized in that the active ingredient is in form of small granules coated with a film formed upon drying a slow release solution of at least one compound per se known for the preparation of slow release compositions.

10 3. Pharmaceutical composition according to claim 2, characterized in that said at least one compound is selected in the group comprising polyvinylpyrrolidone, shellac, hydroxypropylmethylcellulose, and their mixtures.

4. Pharmaceutical composition according to claim 2, characterized in that said coating has a thickness depending on the programmed release time.

5. Pharmaceutical composition according to claim 4, characterized in that said thickness is formed by subsequent single coating films.

15 6. Pharmaceutical composition according to claim 4, characterized in that said thickness is determined by means of in vitro release tests.

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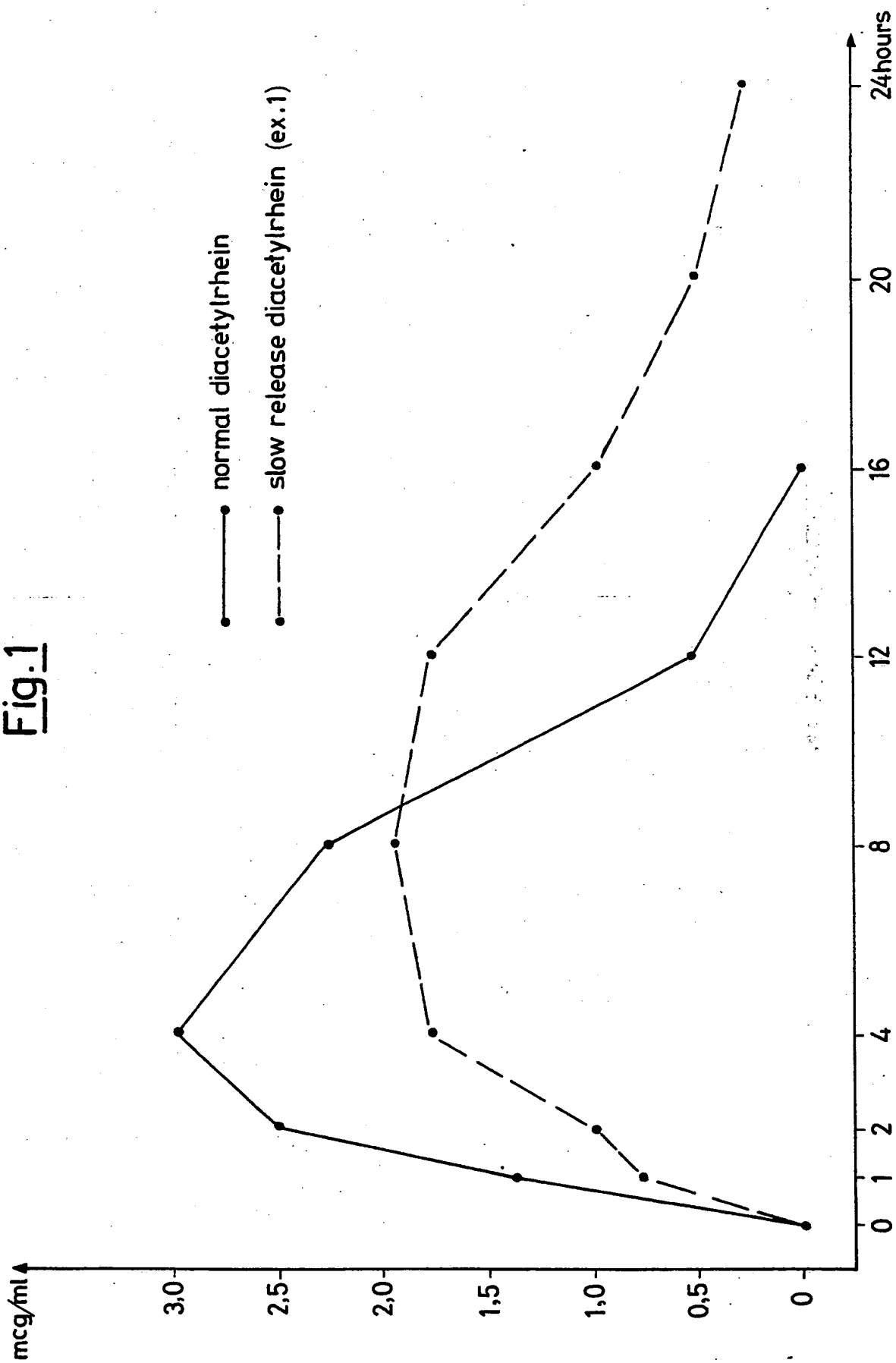
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Fig.1





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EUROPEAN SEARCH REPORT

Application Number

EP 87 20 1845

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	CHEMICAL ABSTRACTS, vol. 100, no. 18, 30th April 1984, page 365, abstract no. 144991e, Columbus, Ohio, US; & JP-A-58 225 015 (PROTER S.p.A.) 27-12-1983 ---	1-6	A 61 K 31/19 A 61 K 31/22 A 61 K 9/52
A	EP-A-0 149 920 (ELAN CORP. P.L.C.) * Page 4, lines 15,19-37; page 5, lines 9-16; page 8, example 2 * -----	1-6	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K C 07 C
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 08-01-1988	Examiner FOERSTER W.K.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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